

Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in Atherosclerosis Progression and Clinical Events

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Objectives. This study was designed to evaluate the effect of pravastatin on progression of coronary atherosclerosis and ischemic events in patients with coronary artery disease and mild to moderate hyperlipidemia.

Background. Few clinical trial data support the use of lipid-lowering therapy in patients with coronary artery disease and mild to moderate elevations in cholesterol levels.

Methods. Four hundred eight patients (mean age 57 years) with coronary artery disease and low density lipoprotein (LDL) cholesterol ≥ 130 mg/dl (3.36 mmol/liter) but < 190 mg/dl (4.91 mmol/liter) despite diet were randomized in a 3-year study to receive pravastatin or placebo. Atherosclerosis progression was evaluated by quantitative coronary arteriography.

Results. Baseline mean LDL cholesterol was 164 mg/dl (4.24 mmol/liter). Pravastatin decreased total and LDL cholesterol and triglyceride levels by 19%, 28% and 8%, respectively, and increased high density lipoprotein cholesterol by 7% ($p \leq 0.001$ vs.

placebo for all lipid variables). Progression of atherosclerosis was reduced by 40% for minimal vessel diameter ($p = 0.04$), particularly in lesions $< 50\%$ stenosis at baseline. There was a consistent although not statistically significant effect on mean diameter and percent diameter stenosis. There were also fewer new lesions in those assigned pravastatin ($p \leq 0.03$). Myocardial infarction was reduced during active treatment (8 in the pravastatin group, 17 in the placebo group; log-rank test, $p \leq 0.05$; 60% risk reduction), with the benefit beginning to emerge after 1 year.

Conclusions. In patients with coronary artery disease and mild to moderate cholesterol elevations, pravastatin reduces progression of coronary atherosclerosis and myocardial infarction. The time course of event reduction increases the potential for a relatively rapid decrease in the clinical manifestations of coronary artery disease with lipid lowering.

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Reduction of total and low density lipoprotein (LDL) cholesterol levels has been shown to be effective in slowing angiographically assessed progression of coronary atherosclerotic plaque and improving clinical outcome in studies of patients with established coronary artery disease (2,3). Most of these trials have used diet alone or in conjunction with multiple drug regimens to reduce serum lipids in patients with relatively

severe hyperlipidemia (2-4). Despite evidence of a clinical benefit, many physicians do not prescribe lipid-lowering therapy for patients with established coronary artery disease (5). In part, the failure to more vigorously detect and treat hyperlipidemia can be attributed to the need for adjustment of dosage, complexity and side effects of multiple drug regimens and the perceived modest benefit on clinical end points (i.e., cardiovascular morbidity and mortality) with strategies before the availability of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (reductase inhibitors). In addition, although substantial evidence attests to a benefit of lipid-lowering therapy for patients with marked hyperlipidemia and coronary artery disease (2,4,6,7), data to support treating patients with more moderately elevated cholesterol levels have not been as convincing. The goal of the present study was to evaluate the effect of a treatment regimen easily adaptable to clinical practice (i.e., monotherapy with a reductase inhibitor, pravastatin, in conjunction with a fat-restricted diet versus a fat-restricted diet alone) on progression of coronary atherosclerosis in patients with mild to moderate hypercholesterolemia and coronary artery disease.

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Methods

The study design, baseline variables and recruitment experience have previously been published (1). The study was a 3-year, multicenter, randomized, double-blind, placebo-controlled trial of pravastatin (40 mg) monotherapy administered once daily. Inclusion criteria were 1) coronary artery disease evidenced by one or more stenoses $\geq 50\%$ or recent myocardial infarction or coronary angioplasty; and 2) average LDL cholesterol concentration ≥ 130 mg/dl (3.36 mmol/liter) but < 190 mg/dl (4.91 mmol/liter) and triglyceride levels ≤ 350 mg/dl (3.95 mmol/liter) despite adherence to a fat-restricted diet (American Heart Association phase I [8] or equivalent) for a minimum of 4 weeks. The protocol was approved by the institutional review board at each study site.

Coronary angiography. The angiographic protocol and quantitative analysis methodology have previously been described (1,9). Matching end-diastolic frames for each of 10 prospectively defined segments (1) were marked on each pair, masked for order and the films forwarded for digitization and quantitative analysis at the core angiography laboratory. In the analysis, if angioplasty or a bypass were performed in one of the three major vessels, that vessel was excluded. The left main stem was excluded in cases of mechanical intervention in the left anterior descending or left circumflex coronary artery. Measurements of mean and minimal diameter and, if applicable, percent diameter stenosis were made for each evaluable segment. Segments with a total occlusion were assigned a value of 0 (for mean and minimal diameters) or 100% (for percent diameter stenosis), including segments with total obstruction at baseline that recanalized. No values were imputed for segments distal to a total obstruction. Angiograms obtained > 90 days after randomization were eligible for inclusion in the analysis (1) as predefined in the protocol. The primary angiographic end point was mean coronary artery diameter (1).

Clinical events. The following clinical outcomes were defined prospectively before study unblinding: fatal or nonfatal myocardial infarction; nonfatal infarction or coronary heart disease death; nonfatal infarction or death from any cause; and total clinical events (nonfatal myocardial infarction, nonfatal completed stroke, death, angioplasty or coronary bypass surgery). For cases of myocardial infarction, death and stroke, documentation was reviewed by an independent Clinical Events Adjudicating Committee.* Classification of myocardial infarction was based on criteria that incorporated the presence of ischemic chest pain, elevation in the cardiac creatine kinase (CK) isoenzyme fraction and evolution of electrocardiographic changes. Coronary heart disease and noncardiac deaths were documented from a death certificate, coroner's report or autopsy report, with supporting hospital records if available; the documentation was reviewed and the cause of death

classified by the adjudicating committee. Coronary angioplasty and bypass surgery were documented by hospital records. A prospectively defined subset analysis was performed for clinical events occurring during the period from > 90 days after randomization to the end of the study, in parallel with the angiographic assessments.

Lipid and lipoprotein levels. Plasma concentrations of total cholesterol, high density lipoprotein (HDL) cholesterol (separated by heparin-manganese chloride precipitation) and glycerol-blanked triglycerides were determined using automated enzymatic methods (Miles-Technicon) at the Lipid Research Center, Washington University School of Medicine; LDL cholesterol was calculated using the Friedewalde formula.

Statistical evaluation. Baseline characteristics of patients in the two treatment groups were compared by one-way analysis of variance (continuous variables) and chi-square tests (categorical variables). Quantitative angiographic outcome variables, calculated as annual rates of progression averaged over all evaluable segments, were analyzed by analysis of covariance. Consistency of results across sites was assessed by testing a treatment-by-site interaction term at the 10% significance level. Clinical events were analyzed by the Kaplan-Meier method and log-rank test. Patients lost to follow-up were treated as censored at the last visit. The association between on-trial plasma lipoproteins (average values of LDL cholesterol and LDL/HDL cholesterol ratio during the study) and progression of atherosclerosis was examined by correlation coefficients (Pearson's product-moment correlation and Spearman's rank correlation) and linear regression analysis. Other risk factors such as age, gender and systolic blood pressure were examined in a stepwise selection procedure to determine a set of independent variables in predicting progression. To assess the association of time to clinical events with lipoprotein levels (posttreatment average), the log-rank test based on exponential scores was used. Effects of risk factors (as previously stated) were also examined using the SAS PROC LIFETEST. The average lipid levels of follow-up visits were analyzed by analysis of covariance. All tests were two-sided.

Results

Patient disposition. Baseline demographic features are shown in Table 1. Evaluable follow-up angiography was obtained in 320 of the 408 patients randomized, including 56 of 141 subjects who discontinued the study drug at some time during the trial. The most common reason for discontinuing the study medication was coronary artery bypass graft surgery (a study end point); 17 pravastatin-treated and 21 placebo-treated patients discontinued therapy for this reason. Other causes for discontinuing the study medication or lack of follow-up angiography were similar between treatment groups except for physician request, which was more common in the placebo group ($n = 10$ vs. 0 in the pravastatin group). Two patients in each group were discontinued for noncompliance with the protocol, as judged by the investigator. Mean (\pm SD)

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Table 1. Baseline Cardiovascular Risk Factors and Demographic and Angiographic Variables

	Pravastatin (n = 206)	Placebo (n = 202)
Male gender	79	76
Current smoker	19	14
Hypertension	47	44
Family history of atherosclerosis	51	56
Prior MI	46	41
Prior angioplasty	55	55
Prior coronary artery bypass	3	6
Medications		
Aspirin	67	71
Calcium blocker	67	63
Beta-blocker	35	39
ACE inhibitor	7	8
Total no. of segments*	1,433	1,400
% distribution of lesions		
≤15	338	349
16-30	449	433
31-50	436	409
51-75	132	141
75-100	24	15
100	54	53
Mean vessel diameter (mm)†	2.58 (0.51)	2.60 (0.50)
Minimal vessel diameter (mm)†	2.03 (0.46)	2.07 (0.46)
% diameter stenosis†	29 (9.65)	28 (9.96)

*Includes all segments in 320 patients with evaluable follow-up angiography.
†Excluding vessels with bypass surgery and angioplasty. Unless otherwise indicated, data presented are percent of patients or mean value (SD). ACE = angiotensin-converting enzyme; MI = myocardial infarction.

follow-up for patients randomized to the placebo and pravastatin groups was 826 ± 373 and 884 ± 348 days, respectively. The average dose of pravastatin was 39 mg daily.

Lipid levels. There were significant and sustained decreases in plasma levels of total (baseline 231 mg/dl [5.97 mmol/liter]) and LDL cholesterol (baseline 164 mg/dl [4.24 mmol/liter]) and triglycerides (baseline 166 mg/dl [1.87 mmol/liter]) and an increase in HDL cholesterol (baseline 41 mg/dl [1.06 mmol/liter]) during pravastatin treatment compared with placebo. In the pravastatin group, the average percent changes from baseline were as follows: total cholesterol -19%, LDL cholesterol -28%, HDL cholesterol +7% and triglycerides -8% (all $p < 0.001$ vs. placebo). In the placebo group, the corresponding changes were +2%, +1%, +2% and +9%, respectively. Average compliance in patients taking the study drug (as assessed by pill counts) was 95% in both groups.

Angiographic progression rates. Follow-up angiography was obtained in 320 patients. The total number of evaluable segments was 1,084 (mean 6.7/patient) and 1,035 (mean 6.6/patient) in the pravastatin and placebo groups, respectively. Angiographic progression rates were reduced by 40% to 50% among patients randomized to receive pravastatin compared with those receiving placebo. In the placebo group, mean and minimal diameters decreased by 0.04 and 0.05 mm/year, respectively. In the pravastatin group, the corresponding decreases were 0.02 mm/year ($p = 0.16$) and 0.03 mm/year ($p =$

0.04). Percent diameter stenosis increased in the placebo group by 1.12%/year versus 0.69%/year in the pravastatin group ($p = 0.13$). If total occlusions are excluded from the analysis, then for mean and minimal diameters and percent diameter stenosis, $p = 0.09$, 0.02 and 0.05, respectively. Progression of atherosclerosis was found to be correlated with both on-trial average LDL cholesterol and the ratio of LDL to HDL cholesterol. For the LDL/HDL cholesterol ratio, the correlation coefficients were small but statistically significant for mean diameter ($r = -0.12$, 95% confidence interval [CI] -0.23 to -0.01) and minimal diameter ($r = -0.15$, 95% CI -0.25 to -0.04). Correlation coefficients were similar for average on-trial LDL cholesterol alone. Inclusion of non-HDL cholesterol in the model did not affect the result. Regression analysis indicates that every 22 mg/dl (0.59 mmol/liter) increment in LDL cholesterol results in 0.01 mm/year of additional narrowing in minimal lumen diameter within the observed on-trial range of 70 to 218 mg/dl (2.02 to 5.64 mmol/liter). Doubling the LDL cholesterol level from 100 mg/dl (2.59 mmol/liter) to 200 mg/dl (5.17 mmol/liter) increases the rate of progression of minimal diameter 3.5-fold. When competing risk factors (age, gender, systolic blood pressure) were examined for joint effects of covariates, LDL cholesterol remained the most important predictor for progression of coronary atherosclerosis.

In a predefined subset analysis according to baseline lesion severity, the major effect of pravastatin was to inhibit angiographic progression of coronary artery disease in segments with lesions <50% diameter stenosis at baseline and to reduce new lesion formation ($p \leq 0.03$ vs. placebo) (Fig. 1). There were no statistically significant differences in progression rates in segments with baseline stenosis $\geq 50\%$.

The distribution of patients with progression, regression, mixed progression/regression or no change for minimal diameter and percent diameter stenosis is shown in Table 2. Progression was defined as progression in at least one segment and no evidence of regression. Regression was defined similarly. Results are given for the cutoff values defined at the beginning of the trial of 0.62 mm for minimal diameter and $\geq 16\%$ for percent diameter stenosis and also for the cutoff points of 0.40 mm and $\geq 15\%$ described by other investigators (10,11). For percent diameter stenosis, progression defined by an increase $\geq 15\%$ has been shown to be related to future risk of coronary heart disease death (12). The results indicate fewer patients with progression in the pravastatin-treated group but similar rates of regression.

Clinical events. Clinical cardiovascular event rates were significantly reduced among patients randomized to receive pravastatin (Table 3), primarily through a reduction in the event rate for myocardial infarction (fatal and nonfatal: log-rank, $p \leq 0.05$; risk reduction 60%). For events occurring during the period from 90 days after randomization to the end of the study, $p \leq 0.01$ (risk reduction 74%). As shown in Figure 2, the curves for myocardial infarction in the pravastatin and placebo groups begin to diverge after the first year. There were 10 total deaths, 6 (5 after 90 days on trial) in the placebo group and 4 (all after 90 days) in the pravastatin group. When risk

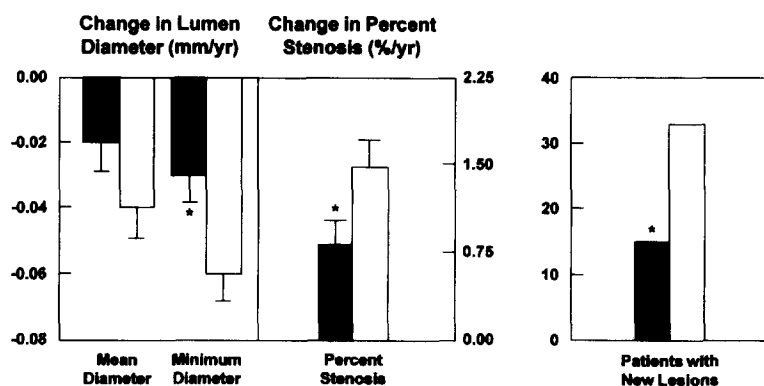


Figure 1. Effect of pravastatin (solid columns, $n = 163$) on angiographic progression rates in lesions with $<50\%$ stenosis at baseline and on new lesion formation versus placebo (open columns, $n = 157$). The major effect of pravastatin was to reduce progression in lesions $<50\%$, as shown by the changes in minimal diameter and percent diameter stenosis. Fewer patients treated with pravastatin developed new lesions, defined as an increase by at least 16% diameter stenosis in a segment with a baseline stenosis $<16\%$. Results are shown as mean change (columns) with standard error (vertical bars). A negative number for mean and minimal diameters and a positive number for percent diameter stenosis indicate progression. * $p \leq 0.03$. For mean diameter, $p = 0.07$ for pravastatin versus placebo.

factors (LDL cholesterol, LDL/HDL cholesterol ratio, age, gender and systolic blood pressure) were examined for joint effects of covariates, only average on-trial LDL cholesterol was identified to be associated with time to infarction, although it was only marginally significant ($p = 0.09$). The relation was negative, suggesting that lower LDL cholesterol levels are associated with a longer infarction-free period.

Clinical events were also evaluated in special subgroups of interest where there is current debate about the benefits of lipid-lowering therapy: the elderly ($n = 94$), patients with baseline LDL cholesterol <160 mg/dl (4.13 mmol/liter, $n = 177$) and women ($n = 92$). There was a trend in favor of pravastatin in each of these groups, and for myocardial infarction the difference was statistically significant among women. For those ≥ 65 years old, among the 52 patients receiving placebo, there were 17 events in 11 patients (6 myocardial infarctions [log-rank, $p = 0.21$ vs. pravastatin], 1 sudden death, 1 noncardiac death, 2 strokes and 1 angioplasty and 6 bypass surgery procedures). Among the 42 patients receiving pravastatin, there were eight events in eight patients (two myocardial infarctions, one noncardiac death and two angioplasty and three bypass surgery procedures). In the subgroup with baseline LDL cholesterol <160 mg/dl (4.13 mmol/liter), among the 92 patients receiving placebo there were 33 events in 23 patients (9 myocardial infarctions [log-rank, $p = 0.09$ vs. pravastatin], 1 sudden death, 1 noncardiac death, 1 noncardiac death, 1 stroke and 12 angioplasty and 9 bypass surgery procedures). In the 85 patients receiving pravastatin, there

were 25 events in 21 patients (3 myocardial infarctions, 1 sudden death and 9 angioplasty and 12 bypass surgery procedures). For the 92 women, among the 48 patients receiving placebo there were 12 events in 5 patients (4 myocardial infarctions [log-rank, $p = 0.04$ vs. pravastatin], 1 noncardiac death, 1 stroke and 3 angioplasty and 3 bypass surgery procedures). Among the 44 women receiving pravastatin, there were five events in five patients (two angioplasty and three bypass surgery procedures).

Drug safety. Therapy with pravastatin was well tolerated. Adverse events occurred with similar frequency in both groups except for dyspepsia/heartburn, which occurred more frequently in the pravastatin group (17% of patients vs. 9% in the placebo group, $p \leq 0.05$). The syndrome of drug-induced myopathy (myalgia and increase in CK levels to >10 times the upper limit of normal) was not observed in any patient. Mean values for aspartate aminotransferase and alanine aminotransferase were slightly (2 to 4 IU/liter) elevated from baseline in the pravastatin group at most annual follow-up visits ($p \leq 0.05$ vs. placebo), although no patient receiving pravastatin was discontinued for an increased transaminase level.

Discussion

As predicted from previous studies (6,7,11,13-18), the decrease in LDL cholesterol and increase in HDL cholesterol with pravastatin in the present study of patients with mild to moderate hyperlipidemia were associated with a reduction in

Table 2. Proportion of Patients With Angiographic Progression and Regression

	Percent Stenosis				Minimal Vessel Diameter			
	Cutoff Value $\geq 15\%$		Cutoff Value $\geq 16\%$		Cutoff Value ≥ 0.40 mm		Cutoff Value ≥ 0.62 mm	
	Pravastatin ($n = 163$)	Placebo ($n = 157$)	Pravastatin ($n = 163$)	Placebo ($n = 157$)	Pravastatin ($n = 163$)	Placebo ($n = 157$)	Pravastatin ($n = 163$)	Placebo ($n = 157$)
Progression	42 (26)*	59 (38)	42 (26)†	55 (35)	60 (37)*	79 (50)	46 (28)	58 (37)
Regression	22 (14)	22 (14)	19 (12)	19 (12)	34 (21)	24 (15)	17 (10)	13 (8)
Mixed progression/regression	20 (12)	21 (13)	15 (9)	19 (12)	26 (16)	30 (19)	7 (4)	9 (6)
No change	79 (48)*	55 (35)	87 (53)*	64 (41)	43 (26)*	24 (15)	93 (57)	77 (49)

* $p \leq 0.03$. † $p = 0.07$. Data presented are number (%) of patients.

Table 3. Effects of Pravastatin on Cardiovascular Events

	All Events After Randomization		Events After 90 Days	
	Pravastatin (n = 206)	Placebo (n = 202)	Pravastatin (n = 206)	Placebo (n = 202)
MI (nonfatal/fatal)	8 (7/1)*	17 (16/1)	5 (4/1)†	17 (16/1)
Other cardiac death‡	2	2	2	1
Stroke	0	2	0	2
Bypass surgery	20	23	15	20
Coronary angioplasty§	25	37	20	29
Total cardiovascular events	55	81	42	69
Noncardiovascular deaths	1	3	1	3

* $p \leq 0.05$, † $p \leq 0.01$ versus placebo. ‡Includes three sudden deaths (two in placebo group, one in pravastatin group) and one resuscitated cardiac arrest (pravastatin group). §Includes more than one event/patient. Data presented are number of events. MI = myocardial infarction.

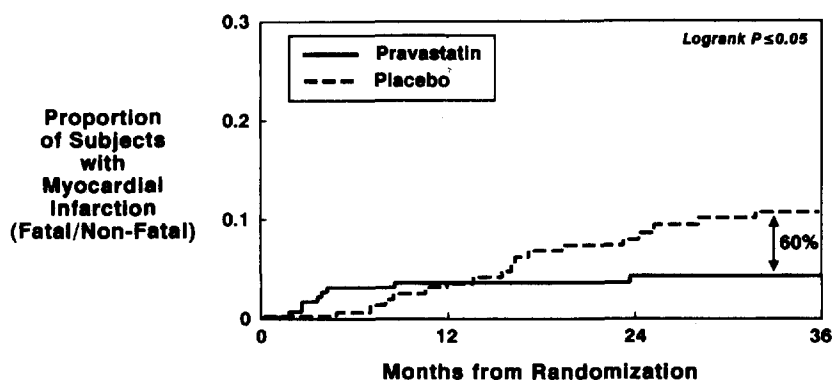
angiographically assessed minimal coronary artery diameter relative to placebo. These effects were most marked in mild lesions (<50% diameter stenosis at baseline) and in preventing new lesion formation (Fig. 1). Progression and rupture of mild coronary artery lesions and new lesion formation are now recognized to be important in the pathogenesis of myocardial infarction (19-22).

Time course of clinical event reduction. What was not predicted on the basis of previous studies of LDL cholesterol reduction before availability of the reductase inhibitors was the time course of the reduction in myocardial infarction event rate in the current study. Law et al. (3), in a meta-analysis of older secondary prevention studies, found only a 7% reduction in ischemic events during the first 2 years of lipid-lowering therapy on the basis of a 10% reduction in total cholesterol. However, in the present study close to a 50% reduction in events (infarction) was observed at 2 years for a 19% decrease in total cholesterol. Most of the reduction in recurrent ischemic events in the meta-analysis of Law et al. (3) occurs during the second to fourth years of somewhat modest reductions in lipid levels. The relatively early reduction in ischemic events observed in the present study has also been seen in other recent monotherapy trials with pravastatin—the Pravastatin

Multinational Study in Cardiac Risk Patients (23), the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC II) trial (24) and the Scandinavian Simvastatin Survival Study (4). The explanation for the relatively early reduction in ischemic events with these reductase inhibitors when used as monotherapy is unclear. The degree of LDL cholesterol reduction seen in those studies is similar to that found in trials such as the Program on the Surgical Control of the Hyperlipidemias study (7), in which a lag phase of up to 3 years occurred before an effect on events began.

Potential mechanism for clinical event reduction. Plaque stabilization affecting mild and new lesions, which is thought to result from a decrease in the lipid content of plaques consequent to sustained reductions in LDL cholesterol is probably of importance in the effectiveness of various lipid-lowering regimens in decreasing ischemic events. However, a reduction in LDL and total cholesterol is also associated with normalization of endothelial dysfunction, which occurs in the presence of hypercholesterolemia with or without manifest coronary artery disease (25-28). Cholesterol reduction with both cholestyramine (29) and the reductase inhibitors (27,28,30) has been shown to reverse endothelial dysfunction in patients with coronary artery disease within 6 months (27,29,30). This

Figure 2. Effect of pravastatin on rate of nonfatal and fatal myocardial infarction from time of randomization: Kaplan-Meier estimate. An effect on the event rate begins to emerge after 1 year of treatment.



mechanism may also directly modify the propensity to plaque rupture, platelet deposition after plaque rupture, thrombosis and progression of coronary atherosclerosis. A reduction in LDL cholesterol might also reduce monocyte migration into the arterial wall and hence the tendency for plaque rupture (31).

Another possibility that could contribute to the relatively early reduction in myocardial infarction by pravastatin is its effect on platelet-induced thrombosis (32). Lam et al. (33) pointed out that patients with enhanced thrombin-induced platelet aggregation have a more rapid angiographic progression of coronary artery disease as well as a significantly increased incidence of ischemic events.

Many clinicians have been hesitant to apply lipid-lowering or dietary therapies because of the perceived long delay in their effectiveness. This perception has largely been fostered by the observation that induction of morphologic changes in the coronary artery tree takes a long time. However, data showing a relatively early reduction in symptoms (5,6), myocardial infarction and ischemic events (23,24) as well as total mortality (4) with reductase inhibitors or a Mediterranean diet (34) suggest that these types of interventions are appropriate for early treatment of asymptomatic as well as symptomatic patients with ischemic heart disease.

There is a need to determine whether a further reduction in LDL cholesterol beyond that achieved in the current study or the Scandinavian Simvastatin Survival Study (4) would be more effective. It should be pointed out that only 14% of the pravastatin-treated patients in the present study reached the National Cholesterol Education Program (NCEP) Adult Treatment Panel II (35) goal of a reduction in LDL cholesterol to <100 mg/dl (2.59 mmol/liter). Multiple drug regimens as used in the Familial Atherosclerosis Treatment Study (FATS) (6) and other angiographic trials (14,15) have achieved a greater reduction in LDL cholesterol and progression of coronary artery disease, along with evidence of coronary artery disease regression. In addition, an early reduction in ischemic events was noted in the FATS (6), although there was no effect on myocardial infarction. It should be noted that the baseline LDL cholesterol values in the multiple-drug therapy studies were also considerably higher than those in the present trial. Further studies are required to determine whether multiple-drug regimens, with the attendant greater reductions in LDL cholesterol, result in greater and earlier decreases in events compared with pravastatin monotherapy as used in the present study.

Conclusions. There is increasing evidence for a benefit of lipid-reducing drugs and dietary strategies for the secondary prevention of ischemic heart disease (2-4). Patients with known coronary artery disease and elevated serum LDL cholesterol levels >130 mg/dl (3.36 mmol/liter) should be placed on an effective diet and drug therapy, preferably a reductase inhibitor. A Mediterranean diet (34) and life-style changes (36) might be more desirable than pharmacologic lipid-lowering therapy alone. However, for those patients who cannot adhere to or respond slowly or inadequately to such

diet or life-style changes, therapy with a reductase inhibitor should be considered.

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